Eur Radiol (2008) 18: 2705–2708
DOI 10.1007/s00330-008-1158-8

EDITORIAL

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CTPA for the diagnosis of acute pulmonary embolism during pregnancy

Received: 5 August 2008
Accepted: 5 August 2008
Published online: 16 September 2008

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Abstract CT pulmonary angiography (CTPA) has been suggested by the Fleischner society as the first test following a negative leg ultrasound in pregnant patients with suspected pulmonary embolism. This editorial discusses the use of CTPA as a diagnostic tool in pregnant women and comments on the need for specifically adapting CT protocols during pregnancy in the light of new research describing a substantial number of non-diagnostic examinations in pregnant women if routine scanning protocols are used for CTA of the pulmonary arteries. Potential reasons for these high numbers of insufficient examinations are physiological changes occurring during pregnancy that lead to a hyperdynamic circulation, which reduces average enhancement of the pulmonary vasculature. In addition, there are possible breathing-related effects that include an increased risk for Valsalva manoeuvre with devastating effects for pulmonary vascular enhancement. Techniques to overcome these problems are discussed: bolus triggering with short start delays, high flow rates or high contrast medium concentration, preferential use of fast CT systems and the use of low kVp CT techniques. CT data acquisition during deep inspiration should be avoided and shallow respiration may be considered as an alternative to suspended breathing in this patient group. All these factors can contribute to optimization of the quality of pulmonary CTA in pregnant patients. It is time now to adapt our protocols and provide optimum care for this sensitive patient group.

Keywords Pregnancy · Acute pulmonary embolism · CT angiography · Radiation dose · Image quality · Contrast injection

Venous thrombo-embolic disease has a two- to fourfold increased incidence during pregnancy and is a leading cause of maternal mortality. Ultrasound of the leg veins has been advocated as the first clinical test for suspected non-life-threatening thrombo-embolism (Statement of the Fleischer Society [1]) because further radiographic imaging is only required if leg ultrasound is normal. The question of which technique to use next for pregnant patients with suspected thrombo-embolism has been hotly debated.

Most investigators recommend CT pulmonary angiography (CTPA) as the appropriate next test, but ventilation-perfusion scintigraphy or half-dose perfusion scintigraphy alone are still being discussed [2–4]. Relatively little focus

has been put on MRA of the pulmonary arteries because of the considerable level of expertise that needs to be permanently available [5]. The argument that CTA is not only able to directly demonstrate the embolus but also detect or rule out alternative reasons for the patient's symptoms is a strong argument in favour of CTA. However, small peripheral emboli that only manifest as a wedge-shaped perfusion defect might be missed. Despite all the limitations, it is generally considered safe to withhold anticoagulation in case of either a normal CTA or perfusion scan [6, 7].

Radiation dose is an important argument in the discussion about the most appropriate technique, but fetal dose with any of the present techniques is well below the dose levels above which a significantly increased risk for congenital abnormality has been proposed [8, 9]. Independent of the fact that radiation dose is already relatively low, any further reduction is welcome in the setting of pregnancy because most of the risks of low-level radiation are difficult to quantify and the risk of malignancy is known to be increased in persons that have been exposed to radiation in utero [10]. CTA has the intrinsic advantage that the fetus is not directly exposed. In perfusion scintigraphy, the need for intravenous injection of the radionucleotide tracer will lead to perfusion-dependent direct fetal exposure. Fetal exposure with CTA is, therefore, lower than exposure with perfusion scintigraphy, even if a half-dose scintigraphic technique is used [11, 12]. There is, however, an underestimated radiation risk associated with pregnant women: the proliferating breast tissue during pregnancy is exposed directly. Because of the fact that the breast tissue is located close to the skin, the breast dose is higher by a factor of 2 than the effective dose given in the usual discussions in the literature [13]. Whether this translates into a measurable increase in breast cancer risk is not yet known. Radiation dose with CTA, however, is strongly dependent on the chosen examination parameters: by optimizing scanning technique, for example by using low kVp settings [14], radiation dose can be reduced and vascular contrast can be increased.

The effect of iodinated or gadolinium-based contrast agents on the fetus and the mother has been discussed [15]. Although there is no indication of fetal or maternal damage in patients with normal renal function, it is agreed that the volume of contrast material should be kept as low as reasonably possible [15].

Despite the fact that there is growing consensus that CTPA should be the next test after leg ultrasound in pregnant patients with suspected pulmonary embolism, there are no large-scale studies evaluating the efficacy of CTPA during pregnancy yet. In clinical practice, however, CTPA in pregnant women appears to be less robust than expected because of variable image quality. This clinical observation has been investigated by two retrospective studies published in this issue of European Radiology [16, 17]. Both studies found—by subjective evaluation and objective quantification—a significantly lower enhancement of the pulmonary arteries in pregnant women than in non-pregnant women of comparable age.

Although the two studies differ with respect to scan speed, examination protocols and methods of image evaluation, the reduction of contrast enhancement (mean 259 HU in pregnant vs 371 HU in non-pregnant women [17]) and the increase in number of inadequate exams was marked and statistically significant (7.5% vs 27.5% [16]). One study even noted a higher number of segments that could not be properly evaluated (13.3% vs 28.7%, $p=0.0001$ [16]), a fact that has a potential influence on the ability of CTA to rule out embolism. This reduced contrast enhancement in pregnant women can have a number of reasons: hyperdynamic circulation with increased cardiac output, increased plasma volume, increased body weight and more pronounced effects of a Valsalva manoeuvre.

Cardiac output increases during pregnancy initially due to increased heart rate, later followed by an increase of stroke volume as well [18]. Cardiac output of up to 50% above non-pregnant levels [19] will lead to stronger dilution of contrast media during the first pass and will lead to proportionally lower contrast enhancement. Plasma volume increases with pregnancy but also with body weight and leads to dilution of contrast material during the recirculation phase. These physiological changes start to take place already within the first trimester and increase within the last trimester [20]. The effects of cardiac output and plasma volume on enhancement were predicted theoretically and verified in an animal model by Bae and co-workers in the 1990s [21]. Although these publications have focussed on the systemic and not the pulmonary circulation, the following assumptions can be derived from these studies:

- Arrival time of contrast material (10% of peak enhancement) is inversely related to cardiac output and flow rate of contrast injection
- Contrast enhancement peaks after a time interval that is identical to the injection time
- Peak enhancement increases with iodine delivery rate (iodine concentration and flow rate) and with total iodine (iodine concentration and contrast volume)
- Peak enhancement is inversely proportional to cardiac output and body weight

Most of these assumptions have found their way into the way modern contrast injection protocols are designed [22, 23]. The effects of cardiac output, however, have not been included in most protocols because it is difficult to establish cardiac output non-invasively prior to a CT examination. Test bolus techniques, which could serve that purpose, have not been widely adopted in clinical routine application [24]. As a consequence, contrast injection protocols for pulmonary CTA have not taken into account the physiological changes occurring during pregnancy, with the result that many routine examinations (7.5% vs 27.5% [16]) are not fully diagnostic. The authors of the two

studies published in this issue [16, 17] have to be congratulated for drawing attention to the need for adaptating contrast injection protocols in pregnancy.

How would such an adaptation look? Because of the increased cardiac output, contrast material will arrive earlier and peak enhancement will be lower than in non-pregnant women. As a consequence, start delays have to be shortened while iodine delivery rates have to be increased. A fixed start delay of 20 s as used by ref. [17] is no longer appropriate: bolus triggering, because of the shorter delay ideally located in the pulmonary trunk, will allow for compensating for the intra-individual variations and guarantee that no extra contrast material needs to be injected to ensure good enhancement with variable contrast arrival times. Iodine delivery rates can be increased by choosing a contrast agent with higher iodine concentration (350–400 mg/ml) or by increasing the flow rate of contrast injection. With the advent of multidetector CT, flow rates have been continuously increased and initial fears of contrast extravasation at high flow rates have been overcome. However, to compensate for an increase in cardiac output by 50%, the flow rates need to be raised from 4 ml/s to 6 ml/s. A combined approach, with increased flow rate and contrast concentration, therefore appears warranted. Such an approach should be able to compensate for the 35% decrease in enhancement seen in the study by ref. [17]. An increase in flow rate, however, also requires an increase in contrast volume to ensure that contrast enhancement does not decrease prematurely. In order to minimize the amount of contrast agent injected, the injection time should be adapted to scan duration and start delay after contrast arrival in the pulmonary artery. Given the hyperdynamic state in pregnant patients, a short start delay of 4–5 s after reaching the trigger level appears appropriate. Injection time then will depend on the speed of the scanner: a four-slice scanner with 20-s scan duration will require substantially more contrast volume than a 64-slice scanner with 5-s scan duration. At a flow rate of 6 ml/s that translates into contrast volumes of 150 ml (25 s at 6 ml/s) for four-slice scanners and 60 ml (10 s at 6 ml/s) for 64-slice scanners. The fastest available scanner should, therefore, be chosen for pregnant patients.

In clinical practice, adaptation of contrast injection to scanner type or even individual patients is frequently not performed. Ref. [16] used the same contrast injection protocol for their 16-slice and 64-slice scanner despite the fact that the 64-slice scanner was trice as fast. Ref. [17] used fixed delays and a long contrast injection on their four-slice scanner. Flow rates varied between 3 ml/s and 4 ml/s. Most patients were studied with standard 300 mg iodine/ml contrast concentration. In one study, contrast protocols were quite variable [17]. These parameters reflect current clinical practice that frequently yields sufficient results for elderly and non-pregnant patients. The substantial increase in cardiac output than can be expected in young pregnant women will lead to the substantial detrimental effects on image quality described by the two groups of authors. These effects ranged from significantly reduced average enhancement (259 HU vs 371 HU [17], 230 HU vs 275 HU [16]) to diagnostically insufficient enhancement in up to 28.7% vs 13.3% of segmental arteries [16] and to a significantly higher number of scans (27.5% vs 7.5%) that were considered non-diagnostic [16]. Given optimized contrast injection protocols to start with, these effects would probably have been less pronounced.

There are other factors, however, that cannot be controlled by contrast injection protocols alone. Physiological changes in respiration during pregnancy may also contribute to the differences in pulmonary enhancement. Deep inspiration in pregnant women may increase the influx of non-contrasted blood via the inferior vena cava into the right atrium. The risk for and the strength of a Valsalva manoeuvre may increase in pregnant women due to psychological stress factors and higher levels of anxiety. The Valsalva manoeuvre will increase intra-thoracic pressure and substantially lower contrast media influx. The effects are especially devastating for examinations with fast scanners and short and ultra-short examination times. Careful instruction of the patient is necessary. Modest inspiration or even shallow breathing may be preferable over breath-holding after deep inspiration.

Optimization of contrast injection and breathing technique may not be the only way to improve contrast enhancement in this patient group. Low kVp techniques have been shown to substantially increase contrast enhancement as well. In fact, this effect is so pronounced that reducing the tube voltage can more than compensate for the reduction of enhancement found in the present studies. Reducing the voltage from 140 kVp to 100 kVp was shown to increase average main pulmonary artery enhancement by 40% and increase enhancement for small arteries even more [14]. Most studies have used this increased enhancement to reduce radiation dose without affecting signal to noise, but in pregnant women the use of 80–100 kVp—depending on patient size—may help counteract the reduction of contrast enhancement seen in pregnancy.

The two studies published in this issue have, for the first time, highlighted the fact that routine contrast injection protocols for CTA of the pulmonary arteries will lead to a substantial number of non-diagnostic examinations in pregnant women. This fact would re-open the discussion about the best technique for diagnosing pulmonary embolism in pregnant women were there not the option of adapting scanning protocols to overcome this limitation: bolus triggering with short start delays, high flow rates and contrast concentration, preferential use of fast scanners and the use of low kVp scanning techniques. All these factors can further optimize the quality of pulmonary CTA in pregnant patients. It is now time to adapt our protocols and provide optimum care for this sensitive patient group.

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